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Editorial

Two decades of progress in the understanding of Brugada syndrome

Brugada syndrome (BS) is a hereditary arrhythmogenic disease characterized by a coved- or saddleback-type ST elevation in the right precordial lead on a 12-lead electrocardiogram (ECG) and ventricular fibrillation (VF) occurring mainly at night. During the past 2 decades, since Brugada and Brugada [1] first described this peculiar condition, there has been notable progress in our understanding of this syndrome with respect to genetics, epidemiology, electrophysiology, and clinical findings. Hundreds of mutations in more than 12 genes that encode sodium, potassium, or calcium ion channels have been identified in individuals with this condition. The prevalence, incidence, and short-term prognosis of this syndrome have also been clarified. However, the exact reason for its predominance in men and Asian individuals remains unknown, although the effect of testosterone and the higher expression of the transient outward potassium (Ito) current in the right ventricular (RV) epicardium in men and polymorphisms that are found only in Asian individuals are believed to be responsible for this predominance.

The pathophysiological mechanism of this syndrome also remains a matter of debate. There are 2 main theories that explain the mechanism of ST elevation and ventricular arrhythmias: the repolarization hypothesis and the depolarization hypothesis. The repolarization hypothesis has been supported by studies using animal models and relies on Ito-mediated transmural dispersion of repolarization between the RV endocardium and epicardium. This theory provides an explanation for the trigger (phase 2 reentry) underlying the development of VF, ST segment elevation by calcium channel blockers or potassium channel openers, ST segment normalization by quinidine or isoproterenol, and the strong association between spontaneous type 1 ECG and cardiac events. In contrast, the depolarization hypothesis relies on conduction delay in the RV outflow tract caused by structural abnormalities. Although this theory has not been demonstrated in experimental models, various data supporting the existence of RV conduction delay have been obtained from electrophysiological studies (EPS) and clinical studies involving signal-averaged ECGs and body surface, epicardial, and endocardial mapping. Furthermore, Nademanee et al. [2] recently demonstrated that abnormal low-voltage, prolonged, and fractionated late potentials exist in the epicardial aspect of the RV outflow tract in selected BS patients who received multiple shocks by an implantable cardioverter-defibrillator (ICD). It is unknown whether these abnormalities exist in every BS patient and which hypothesis is more reliable. Further research is needed to clarify these issues as well as to determine the efficacy of catheter ablation in patients with BS. The value of VF inducibility by EPS is still a controversial topic for risk stratification in BS. Although many studies have failed to demonstrate the usefulness of EPS, a good association between VF inducibility and patient outcome may be obtained by using specific standardized stimulation protocols, as reported by Makimoto et al. [3].

Thus far, a number of guidelines have been reported based on the results of previous multicenter studies. The Japanese Circulation Society proposed that ICD implantation is indicated for patients without prior VF, when 2 of the following 3 risk factors are present: a history of unexplained syncope, VF inducibility by EPS, and a family history of sudden death. This guideline seems to be appropriate for Japanese Brugada patients. Nevertheless, we should be mindful to recommend "you don't need to implant ICD" to an asymptomatic patient with a typical Brugada ECG but with only one or no risk factor, because there are no available data of long-term follow-up for such patients. During the past 2 decades, research in BS has progressed markedly and we are on a steep learning curve, even though several more years of studies may be required until the day when we can precisely identify low or no risk patients and confidently tell them "you are safe".

References

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